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DOI:

[10.1136/archdischild-2018-316515](https://doi.org/10.1136/archdischild-2018-316515)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Ewer, A 2019, 'Perfusion index cannot be currently recommended as an additional newborn screen for CCHD; more data needed', *Archives of Disease in Childhood*, vol. 104, no. 5, pp. 411-412.
<https://doi.org/10.1136/archdischild-2018-316515>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Checked for eligibility: 01/07/2019

This article has been accepted for publication in Archives of Disease in Childhood, 2019 following peer review, and the Version of Record can be accessed online at: <http://dx.doi.org/10.1136/archdischild-2018-316515>

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Archives of Disease in Childhood

editorial on archdischild-2018-315891.R1 - Does pulsatility index

> add value to newborn pulse oximetry screening for critical

> congenital heart disease ?

Title - Perfusion index cannot be currently recommended as an additional newborn screen for CCHD; more data needed.

Journal:	<i>Archives of Disease in Childhood</i>
Manuscript ID	Draft
Article Type:	Editorial
Edition:	not in use
Date Submitted by the Author:	n/a
Complete List of Authors:	Ewer, Andrew; Birmingham Womens Hospital, Neonatal Unit; University of Birmingham
Keywords:	Neonatology, Cardiology, Pulse oximetry, Newborn screening, congenital heart defect

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Editorial

Perfusion index cannot be currently recommended as an additional newborn screen for CCHD; more data needed.

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Abbreviations: CCHD – critical congenital heart defect, POS – pulse oximetry screening, PI – perfusion index

Word count - 1160

Refs - 5

Conflict of interest: Prof Ewer has received travel and accommodation expenses from Masimo and Medtronic to present at scientific meetings only and has received no personal payments or honoraria from any oximeter manufacturers. He has no financial interests in any oximeter manufacturers.

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3 Routine pulse oximetry screening (POS) of newborn babies before discharge from hospital has been
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5 shown to identifying cases of CCHD with consistent test accuracy¹ and to reduce mortality from
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7 these conditions by one-third.²
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11 There is increasing uptake of POS in high and middle income countries;¹⁻⁴ in July 2018, after several
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13 years of state-by-state introduction, POS became mandatory across the USA² which means that
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15 almost 4 million babies a year will undergo the test in that country alone.
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19 POS reduces the 'diagnostic gap' for CCHD, i.e. it identifies additional cases which are missed by
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21 other screening methods such as antenatal ultrasound and postnatal examination.¹ The size of this
22
23 gap varies depending on local circumstances, but the addition of POS consistently reduces it to less
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25 than 10%.⁴
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29 However, as described in this recent Archimedes article,⁵ POS is not a perfect test. Some babies
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31 (particularly those with defects that obstruct left ventricular outflow such as coarctation of the aorta
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33 [CoA] and interrupted aortic arch[IAA]) are missed by POS and other routine screening tests⁴ and
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35 Searle and colleagues quite rightly ask if an additional screening tool – perfusion index (PI) - could
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37 have identified such defects earlier.⁵
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41 As Searle *et al* describe, PI is an assessment of pulse strength - measured at the same time as oxygen
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43 saturations by a pulse oximeter which calculates the ratio of pulsatile to non-pulsatile blood. Lower
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45 PI values represent reduced perfusion.⁵
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49 Given that critical obstruction of left ventricular outflow is highly likely to affect peripheral perfusion
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51 the suggestion that PI may be a useful adjunct to oxygen saturation screening (in order to increase
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53 detection of those CCHDs which are commonly missed) is not unreasonable.
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56 Although the premise for considering the use of PI in this context is logical and appealing, this review
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58 demonstrates inherent concerns which mean that the case for considering PI as an additional
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60 screening test for CCHD is not yet proven.⁵

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Five studies, which investigated the role of PI in increasing detection of CCHD during routine POS - and including just over 1000 to over 42 000 babies screened - are described in detail.⁴ Three of the five were significantly underpowered, each reporting data from under 3 200 screened babies. The two larger studies reported around 10 000 and 42 000 screened babies.

Measuring PI in 10 000 healthy term newborns between 1 and 120 hours of age (median 42), Granelli *et al* established the normal range for this population; describing a median value of 1.68 (pre-ductal) and 1.71 (post-ductal).⁵ The range was very wide (0.02-20.0), 5th centile was 0.7 and no age-specific differences between values at 1 hour and 5 days were identified. In a much smaller, retrospective study of 2768 babies, Jagatheesen *et al* confirmed similar values for PI in babies at 24 hours of age.⁵

Using the 5th centile as a cut-off for an abnormal value, Granelli showed that five out of nine babies (56%) with a [previously diagnosed] CCHD obstructing left ventricular outflow could be identified using PI. POS alone diagnosed 6 out of 9 although 2 of the 3 missed by POS were identified by PI. Although providing useful data, this study has its limitations, particularly when considering the possibility of using PI as a screening test. The babies with the CCHD already had an established diagnosis and were therefore perhaps a biased group, also PI was measured after 36 hours of age in 56% of those screened which limits the applicability of the data, particularly for POS screening algorithms which recommend screened around the first 24 hours of life.

In a large prospective study from Italy, Schena *et al* measured PI (in addition to performing POS) in over 42 000 asymptomatic babies in whom CCHD was not suspected antenatally.⁵ Again, screening (using a higher PI cut-off value of 0.9) took place later (between 48 and 72 hours of age).

Unfortunately, the prevalence of CCHD in the screened population was very low (76% of CCHD were diagnosed antenatally and 84% of the remainder were diagnosed before screening could take place. Only 7 babies with CCHD (out of a total cohort of 187) were screened and 4 were missed by both

POS and PI (including 2 CoAs and 1 IAA). PI picked up 1 CoA that was missed by POS and the 2 remaining CCHDs were picked up by POS alone.⁵

Finally, two much smaller studies from India and Turkey are reported.⁵ Ramesh *et al* used PI (cut-off value of 0.7) in combination with POS in a cohort of just over 1 000 babies and identified one CCHD (which was also picked up both antenatally and using POS), but missed 2 further cases which were identified by POS. Uyger *et al* retrospectively applied PI to 3 175 babies screened by POS (including 33 with an antenatal diagnosis of a heart defect) using a much higher cut off values of 1.1 for pre-ductal and 1.2 for post-ductal measurements (the 5th centiles in this cohort). POS identified 25 out of 33 CCHD (sensitivity 75.9%) whereas PI with the higher cut-off had a sensitivity for CCHD of 60.6% (post-ductal) and 63.6% (pre-ductal) – including 3 CCHD missed by POS. When the more widely accepted cut off of 0.7 was applied, the sensitivities for PI fell to 33.3% and 36.4% respectively. False positives were also very high – 2.7% (pre-ductal) and 3.6% (post-ductal).

So where does this leave us and how should we use these data? The available evidence suggests that normal PI values seem to be fairly stable and consistent over the first few days of life. What is less clear is the natural history of PI in CCHD particularly left heart obstruction. The rationale behind using PI as a potential screen for these conditions is that perfusion is compromised particularly as the ductus arteriosus closes. The timing of ductal closure is variable and as the number of missed cases highlighted in the review suggest, if the duct is still open in a left heart CCHD, the PI may not be abnormal. Of additional concern is the lack of acceptable 'normal' values for PI in this group and the unacceptably high false positives rates if values below the 5th centile are used as a screening cut-off.

And yet, these studies do show that PI alone will identify *some* babies with CCHD that would otherwise be missed by all other screening methods and so perhaps we should not discount this technique altogether. As was the case with the earlier studies examining POS,¹ we need more data in order to identify more precisely the test accuracy of PI. As more babies worldwide are being

screened using POS, PI data could be collected alongside the saturation results and, if linked with outcome data, may provide the necessary information required. In addition, newer technologies may allow a more rigorous cotside assessment of perfusion and left heart function.

Until then, as Searle and colleagues rightly conclude, we do not have enough evidence yet to recommend adding PI to any newborn POS programme.

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